REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Office Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Claims 1-47 are pending in this application.

Claim 1 has been amended to incorporate the limitations of Claim 10, and Claim 10 has been cancelled.

Claim 5 is amended to recite "wherein above the Tg the first polymer network consists of crosslinked polymer chains inside each nanoparticle, and the second polymer network consists of a crosslinked system of the nanoparticles." This is supported throughout the specification and in paragraphs [0013] and [0056].

Claim 15 has been amended to recite "wherein the first polymer has a low critical solution temperature of between 28°C and 45°C, the first polymerization temperature is above the LCST of the first polymer" and "wherein the nanoparticle solution is an aqueous solution." This is supported throughout the specification and in paragraphs [0007] and [0050].

Claim 18 has been amended to recite "wherein above the Tg the first polymer network consists of crosslinked polymer chains inside each nanoparticle, and the second polymer network consists of a crosslinked system of the nanoparticles." This is supported throughout the specification and in paragraphs [0013] and [0056].

Claim 29 has been amended to correct the spelling of the word "gelation."

I. CLAIM OBJECTIONS

The Examiner has objected to Claim 29 on the grounds that the word gelation is incorrectly spelled "gelationin." Applicants have amended Claim 29 to correct this, and believe that this will overcome the Examiner's objection.

II. CLAIM REJECTIONS UNDER 35 USC §102

The Examiner has rejected Claims 15, 20-22, 24-26, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Bouillot et al. (Colloid Polym Sci, 2000, Vol. 278, p.74-79, "the Bouillot Reference").

The Examiner states that the rejected claims are drawn to a method of preparing an interpenetrating polymer network (IPN) of monodispersed nanoparticles, comprising, providing a first mono-dispersed polymer nanoparticle prepared by mixing a first monomer, a surfactant, a first cross linking agent, and first initiator at a first temperature, adding to the first mono-dispersed polymer nanoparticles a second monomer, a second cross linking agent, a second initiator and an activator, mixing the nanoparticle solution for a period of time at a second temperature to form the IPN on mono-dispersed nanoparticles, isolating the IPN nanoparticles, wherein the first monomer, the first cross linkin g agent, the second monomer, and the second cross linking agent are substantially free from dissolved oxygen gas and the first wherein the first polymer forms a first polymer network which interpenetrates a second polymer network formed by the second polymer, wherein the first polymer comprises poly(-N-isopropylacrylamide) [PNIPAM] and the second polymer comprises poly (acrylic acid), a hydrodynamic radius in the range of 75 nm to about 200 nm, the period of time is less than 130 minutes and is about 120 minutes, and the second temperature at about 21°C.

The Examiner states that the Bouillot Reference anticipates the claimed method because the reference discloses a method of preparing an interpenetrating polymer network (IPN) of monodispersed nanoparticles (p.76, first and second column, 1st paragraph, lines 5-8), comprising, providing a first mono-dispersed polymer nanoparticles prepared by mixing first monomer, a surfactant, a first cross linking agent, and first initiator at a first temperature, adding to the first

mono-dispersed polymer nanoparticles a second monomer, a second cross linking agent, a second initiator and an activator, mixing the nanoparticles solution for a period of time at a second temperature to form the IPN on mono-dispersed nanoparticles, wherein the first polymer comprises PNIPAM and the second polymer comprises poly (acrylic acid), isolating the IPN nanoparticles, wherein the first monomer, the first cross linking agent, the second monomer, and the second cross linking agent are substantially free from dissolved oxygen gas (solutions purged with N_2), period of time is less than 130 minutes and is about 120 minutes, and the second temperature is 25°C (about 21°C)(p.75 2nd column 2nd and 3rd paragraphs), and the first wherein the first polymer forms a first polymer network which interpenetrates a second polymer network formed by the second polymer (p.78 1st column 1st paragraph), hydrodynamic diameter (radius) is 150 nm (in the range of 75 nm to about 200 nm) (p.76 1st column last paragraph lines 10-11).

Applicants respectfully disagree with the Examiner's assessment. **The Examiner's statement that the Bouillot Reference discloses a first polymer comprising PNIPAM is incorrect. In fact, the Bouillot Reference discloses a first polymer comprising polyacrylamide** (PAAm). See: (a) the Abstract; (b) p. 75; (c) Figures 1 and 2; and (d) Table 1. The current Claim 20 recites PNIPAM or hydroxypropylcellulose, and Claim 22 recites PNIPAM, meaning that these claims cannot be anticipated by the Bouillot Reference, which teaches a method which incorporates a differrent composition. Claim 1 has also been amended to emphasize this difference.

The Bouillot Reference teaches that PAAc/PAAm IPN particles were synthesized in two steps, the first step being that pure PAAm particles were synthesized by ***inverse microemulsion polymerization*** (p. 75, 2nd column, 3rd paragraph). The procedure for inverse microemulsion polymerization is described on p. 75, 2nd column, 2nd paragraph of the reference, which states that, "These particles were synthesized by an ***inverse microemulsion polymerization*** route [Citation omitted]. All the polymerization reactions were performed at the same composition: 13.3% surfactant, 81% oil (hexane), 5.7% aqueous solution. In a typical microemulsion polymerization, AOT and Brij 30 were combined in a 33/17 weight ratio and were dissolved in hexane."

In contrast to the ***inverse microemulsion polymerization*** method of the Bouillot Reference, the current method claims (claims 15, 20-22, 24-26, and 28) recite synthesis of PNIPAM particles

using a ***precipitation polymerization method known in the art.*** In the currently claimed method, the pregel solution is an aqueous solution comprising monomers without any oil.

Therefore, a further distinguishing characteristic is that Bouillot Reference teaches a method of producing IPN particles which comprises mixing two polymers in a solution which comprises oil. The current invention requires mixing the two polymers in an aqueous solution. Applicants have amended Claim 15 to emphasize this difference.

As described above, it is clear that the Bouillot Reference describes a polymerization method using PAAm particles, rather than PNIPAM particles as recited in the current claims. One of the major differences between these two polymers is that PAAm is not sensitive to temperature but PNIPAM is very sensitive to temperature. In fact, PNIPAM has a low critical solution temperature (LCST) of about 33°C while the PAAm does not. As a result, there is a significant difference between using PNIPAM and PAAm particles in synthesis. The polymerization was carried out at 70°C above the LCST of the PNIPAM so that the PINPAM polymer precipitated into particles.

The thermosensitive IPN hydrogel particles of the Bouillot Reference show positive swelling, meaning that the gel swells almost linearly with temperature above 20°C (Figures 4 and 5 of Bouillot). In contrast, the IPN hydrogel particles of the current invention shrink slightly with temperature. At the LCST of PNIPAM at 33°C, the particle radius shows clear drop as shown in Fig. 5 of the present application. The behavior of the IPN particles taught in the Bouillot Reference with temperature is due to the broken cooperated hydrogel bonding between PAAm and PAAc, which has a zipper effect at higher temperature. In the IPN particles of the present invention, the shrinking of IPN particles occurs because the PNIPAM changes from a hydrophilic state to a hydrophobic state above the LCST.

A significant difference between the concentrated PNIPAM/PAAc IPN nanoparticles of the current claims and IPN particles of the Bouillot Reference, is that the particles of the current invention in water at pH 7 can change from a fluid state at room temperature to a solid gel state at 37°C. This is due to temperature induced hydrophobic interaction between neighboring particles. There is no mention of this behavior in the Bouillot Reference, and in Figures 4 and 5 of the Bouillot Reference, one can see that the particle size increase with temperature almost linearly. Because of the properties of the particles in the Bouillot Reference, there is no "gelation" temperature

determined by the LCST of the PNIPAM as there is in the present invention. In the Bouillot Reference, there is no temperature induced attraction like hydrophobic interaction in the currently claimed IPN particles. As a result, the neighboring particles can not stick together by attractive force at an elevated temperature.

In order to emphasize this difference between the current claims and the Bouillot Reference, Applicants have amended Claim 15 to recite "wherein the first polymer has a low critical solution temperature of between 28°C and 45°C, the first polymerization temperature is above the LCST of the first polymer" and "wherein the nanoparticle solution is an aqueous solution." Because the Bouillot Reference teaches a method which is not identical to the currently claimed method, it cannot be said to anticipate the current claims. Applicants respectfully submit that Claims 15, 20-22, 24-26, and 28, as amended, are in condition for allowance.

III. CLAIM REJECTIONS UNDER 35 USC §103

A. Claims 1-14 over Bouillot in view of Qui, Cai, and Jeong

The Examiner has rejected Claims 1-14 under 35 U.S.C. 103(a) as being unpatentable over the Bouillot Reference in view of Qiu et al. (Advanced Drug Delivery, 2001, Vol. 53, p.321-339, "the Qui Reference") and further in view of over Cai et al. (Journal of Applied Polymer Science, 2002, Vol. 83, p.169-178 "the Cai Reference") and further in view of Jeong et al. (Advanced Drug Delivery Reviews, 2002, Vol. 54, p.37-51 "the Jeong Reference"). The Examiner states that Claims 1-14 are drawn to an aqueous dispersion of hydrogel nanoparticles comprising, interpenetrating polymer network (IPN) nanoparticles, wherein each IPN nanoparticle comprises a first polymer network interpenetrating a second polymer network, and an aqueous medium, wherein the IPN nanoparticles are substantially free of shell and core polymer configuration, and the aqueous dispersion of hydrogel nanoparticles can undergo a reversible gelation in response to a change in stimulus applied thereon, the aqueous dispersion of hydrogel nanoparticles further comprising a biologically active material, wherein the stimulus comprises a change in temperature, Tg is about 34°C, poly (-N-isopropylacrylamide) and the second polymer comprises poly(acrylic acid), a uniformed sized hydrodynamic radius in the range of 75 nm to about 200 nm, IPN nanoparticles

have weight ratio of about 1:1.88, and total polymer concentration from about 1.25 wt% to about 5.25 wt% in distilled water.

The Examiner states that Bouillot et al. teach a method of preparing an interpenetrating polymer network (IPN) of monodispersed nanoparticles (p.76, 2nd column, 1st paragraph, lines 5-8). The Examiner states that Bouillot et al. teach preparation of IPN particles containing various acrylic acid/acrylamide (AAc/AAm) ratios and different cross-linker amounts (p.75 1st column 4th paragraph).

As described in detail above, the Bouillot Reference teaches the synthesis of polyacrylamide (PAAm) particles, not poly-N-isopropylacrylamide (PNIPAM) particles as recited in the current amended claims. PAAm and PNIAPAM are very different particles, both in terms of the way they can be synthesized (inverse microemulsion polymerization versus precipitation polymerization), and the properties they possess (e.g. swelling in response to increased temperature). Therefore, the teaching of the Bouillot Reference, which related to PAAm, would not have provided a motivation to one of skill in the art to use PNIPAM.

The Examiner goes on to state that Bouillot et al. further teach thermosensitive IPN hydrogels have been synthesized that could be used for control drug release. Bouillot et al. teach the principle of controlled drug release, using ketoprofen as the drug, from PAAc/PAAm IPN hydrogels in response to a temperature (p.75, 1st column, 2nd paragraph), hydrodynamic diameter (radius) is 150 nm (in the range of 75 nm to about 200 nm) (p.76, 1st column, last paragraph lines 10-11).

However, the Bouillot is referencing a different author's work, which also involved PAAc/PAAm IPN hydrogels. As described above, this is a distinct composition from the composition which is described and claimed in the current application. The PNIPAM of the current application has very different properties from the PAAm described in the Bouillot Reference. Moreover, no experimental details are provides as to how PAAc/PAAm IPN hydrogels could be used for controlled release of a drug.

The Examiner goes on to state that, although Bouillot et al. do not teach "wherein ... the aqueous dispersion of hydrogel nanoparticles can undergo a reversible gelation in response to a change in stimulus applied thereon," but states that Qiu et al. teach if the polymer chains in

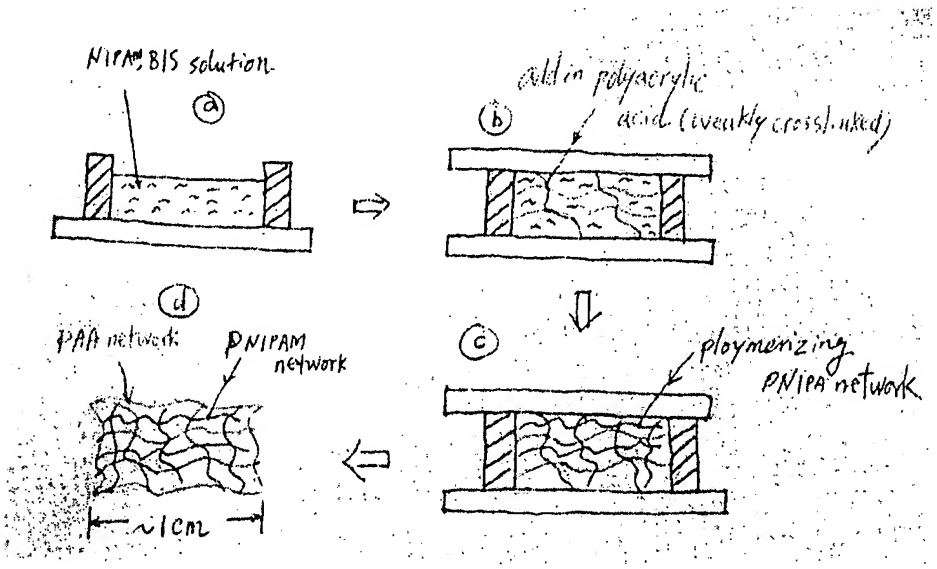
hydrogels are not covalently cross-linked, temperature-sensitive hydrogels may undergo sol-gel phase transitions instead of swelling-shrinking transitions.

The mechanics of gelation taught by Qui et al., however, do not apply to the currently claimed material. The Qiu Reference teaches thermogelation from block co-polymers. The present invention relates to hydrogel nanoparticles, which have entirely different synthesis and characteristics as described above.

The Examiner also states that Cai et al. teach that properties of each network may be maintained in IPN hydrogels. However, Cai et al. (p. 170, 2nd column, 2nd paragraph) explicitly describe ***bulk hydrogels***, rather than the ***hydrogel nanoparticles*** described in the instant application. The teachings of the Cai Reference would not provide one of skill in the art with the motivation to pursue the instantly claimed hydrogel nanoparticle invention.

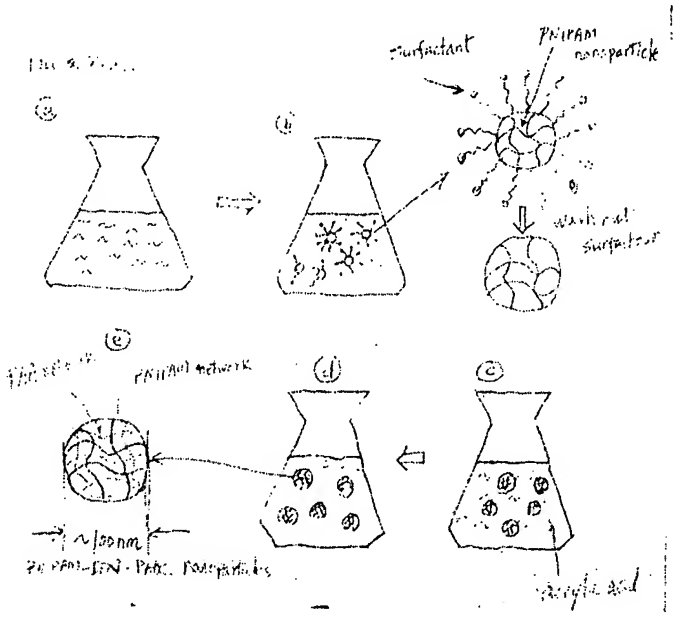
The IPN bulk gels taught in the Cai Reference were synthesized as illustrated below in **Schematic 1:** (a) the first solution including NIPA, and BIS, was added to a glass slide and a gasket; (b) the second solution of polyacrylic acid (that is weakly crosslinked), BIS, initiator, etc, is added into the first solution, and the total solution is sealed using two glass slides with a gasket as a spacer between the two glass slides; (c) polymerization reaction is allowed to proceed to form the interpenetrating polymer networks (IPN) of PAAc and PNIPAM; (d) after removing glass slides and the gasket, the IPN bulk gel was immersed in water.

Schematic 1. Synthesis of bulk hydrogels in the Cai Reference.



The process taught in the Cai Reference is therefore totally different from the currently claimed process to make IPN nanoparticles. The currently claimed method is illustrated below in **Schematic 2:** (a) NIPAM, BIS, surfactant, etc, were mixed in water under nitrogen environment; (b) an initiator is added, and the temperature is increased to 70°C, and then the NIPAM precipitates into spheres surrounded by surfactant, subsequent to the polymerization reaction, the PNIPAM nanoparticle spheres were formed and washed to remove surfactant; (c) the PNIPAM nanoparticles were then immersed in acrylic acid, BIS, and initiator water solution; (d) after polymerization of acrylic acid, nanoparticles of PNIPAM-PAA interpenetrating polymer networks (IPN) formed. The diameter of the IPN nanoparticles is about 100-200 nm.

Schematic 2. Synthesis of bulk hydrogels according to the currently claimed method.



The Examiner states that even further motivation is found in the Jeong Reference, which teaches an aqueous solution of NiPAAM/acrylic acid copolymer showed reversible gelation above a critical concentration around 32°C rather than polymer precipitation (p.40 2nd column 2nd paragraph).

The Jeong Reference teaches (p.40 2nd column 2nd paragraph), that "[i]t was found that an aqueous solution of high molecular-weight NiPAAM/acrylic acid (2-5 mol%) copolymer synthesized in benzene showed reversible gelation above a critical concentration (-4 wt%), without noticeable hysteresis around 32°C, rather than polymer precipitation [Citation omitted]. The polymers were characterized as having a distribution of polymer composition. Gelation was attributed to polymer chain entanglements and the weak physical association of polymer precipitates with fewer ionizable groups at lower temperatures while maintaining hydration by more charged and expanded polymer strands."

It is clear that the Jeong Reference teaches gelation of copolymer of PNIPAM/PAAc. The copolymer was made in benzene. In contrast, the current claims recite hydrogel nanoparticles with two interpenetrating polymer networks of PNIPAM and PAAc. Hydrogel nanoparticles with copolymer of PNIPAM and PAAc in water do not have thermogelation properties.

The gelled copolymer chains in the Jeong Reference can only have one mesh size at an elevated temperature, determined by the distribution of polymer chains. In significant contrast, the gelled IPN hydrogel nanoparticles of the current claims have two mesh sizes in water at body temperature. There are two different networks in a gel nanoparticle network. The primary network is crosslinked polymer chains inside each nanoparticle, while the secondary network is a crosslinked system of the nanoparticles themselves. The mesh size of the primary network depends on the concentration ratio of the crosslinker to linear polymer chains or monomers and is usually around from 1 to 10 nm. In comparison, the mesh size of the secondary network depends on the concentration of the crosslinker and nanoparticles, and the size of nanoparticle. The mesh size is typically around from 50 to 500 nm.

B. Claims 15-20 over Bouillot, Kurisawa, and Qui

The Examiner has rejected Claims 15-20 under 35 U.S.C. 103(a) as being unpatentable over the Bouillot Reference in view of Kurisawa et al. (Journal of Controlled Release, 1998, Vol. 54, p.191-200, "the Kurisawa Reference") and further in view of the Qiu Reference.

The Examiner states again that the Bouillot Reference teaches the limitations of Claims 15, 20-22, 24-26, and 28. As described in detail above, Applicants respectfully submit that the Bouillot Reference does not teach the limitations of Claims 15, 20-22, 24-26, and 28, as amended, because the reference teaches PAAc/PAAm IPN hydrogels, while the instant specification teaches PNIPAM/PAAc IPN nanoparticles. The currently claimed PNIPAM/PAAc IPN nanoparticles have distinct characteristics, including shrinking with increased temperature (Figures 4 and 5 of the instant specification), and a fluid to solid transition at 37°C due to temperature induced hydrophobic interaction between neighboring particles.

Moreover, as described above, the Bouillot makes reference to the Katono Reference, which demonstrated controlled drug release in PAAc/PAAm IPN hydrogels. However, this has not been

taught for the instantly claimed IPN nanoparticles, nor does the Bouillot Reference provide means or motivation for producing the instantly claimed IPN nanoparticles.

As described in detail above, the Katono Reference cited by the Bouillot Reference describes the preparation of a ***bulk*** gel of Interpenetrating polymer networks (IPNs) composed of poly(acrylamide(AAm)-*co*-butyl methacrylate (BMA)) and poly(acrylic acid) (PAAc) and they used this bulk gel for the study of controlled ketofen release. As previously stated, a bulk gel is always a single piece at any temperature even if its size changed with temperature. In contrast, the current invention comprises millions of IPN hydrogel nanoparticles in water. At room temperature, these IPN nanoparticles do not stick together so that the dispersion of the nanoparticles is a liquid. A drug can be mixed into this liquid very easily. Once the temperature of the dispersion is raised above the LCST of about 33°C, the nanoparticles are stick with each other due to temperature induced hydrophobic interaction. The dispersion therefore becomes a solid gel. The drug then is slowly released from this physically gelled assembly of hydrogel nanoparticles.

The Examiner has stated that, although Bouillot et al. do not teach the mixing the isolated IPN of mono-dispersed nanoparticles with a biologically active material at a third temperature, Kurisawa et al. teach a method of preparing an interpenetrating polymer network (IPN)-structured hydrogels of gelatin (Gtn) and dextran (Dex) with lipid microspheres (LMs) as a drug microreservoir (as a model of a drug substrate), the a phase morphology in the IPNstructured hydrogels was varied with the preparation temperature, i.e. above or below the sol-gel transition temperature (Ttran,) of gelatin (Abstract, and p. 194 2nd column 1" paragraph).

Applicants respectfully submit that the mechanics of the ***bulk*** IPN gels taught in the Kurisawa Reference are significantly different than the currently claimed IPN hydrogel nanoparticles. Moreover, gelatin is a liquid at body temperature, and then becomes a solid below the sol-gel transition temperature at around 20°C. The currently claimed IPN hydrogel nanoparticles exhibit the opposite behavior, an ***inverse*** sol-gel transition. That is, below the gelation temperature (or it may be called transition temperature using Kurisawa's convention) of 33°C, the dispersion of the hydrogel nanoparticles is a liquid but becomes a solid above gelation temperature.(Claims 5 &6).

Significantly, the Kurisawa Reference applied the sol-gel transition of the gelatin only for preparing bulk IPN gels. Specifically, the pregel solutions of Dex and Gtn as well as lipid

microspheres (LMs) were mixed together. If the reaction temperature was above the transition temperature, Gtn formed first and then the Dex formed as the second network around Gtn. If the reaction temperature was below the transition temperature of Gtn, Dex formed the first and then Gtn formed as the second network interpenetrating Dex. In both case, lipid microspheres (LMs) were embedded inside bulk IPN gels.

This method of producing a bulk gel is entirely distinct from the currently-claimed method of making IPN nanoparticles, which is shown in **Schematic 2** above: (a) NIPAM, BIS, surfactant, etc, were mixed in water under nitrogen environment; (b) an initiator is added, and the temperature is increased to 70°C, and then the NIPAM precipitates into spheres surrounded by surfactant, subsequent to the polymerization reaction, the PNIPAM nanoparticle spheres were formed and washed to remove surfactant; (c) the PNIPAM nanoparticles were then immersed in acrylic acid, BIS, and initiator water solution; (d) after polymerization of acrylic acid, nanoparticles of PNIPAM-PAA interpenetrating polymer networks (IPN) formed. The diameter of the IPN nanoparticles is about 100-200 nm.

Moreover, the drug release described in the Kurisawa Reference is accomplished by enzymatic degradation of the hydrogels. This is shown in Figure 1 of the Kurisawa Reference. Here single stimulus means one enzyme and due stimuli mean two enzymes.

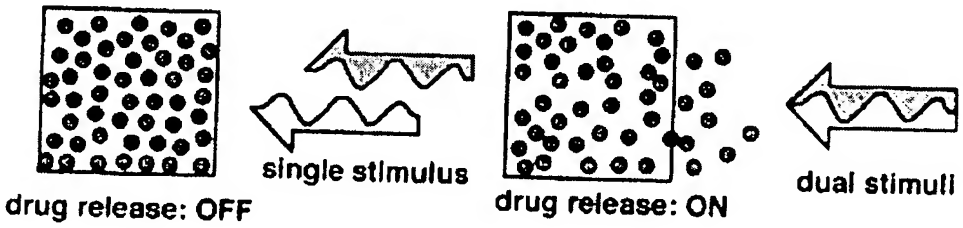


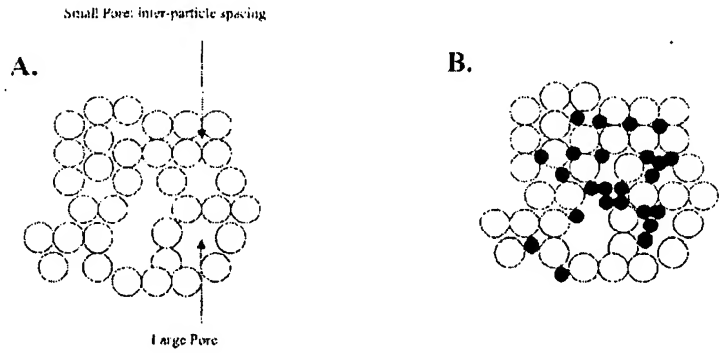
Fig. 1 Concept of dual-stimuli-responsive drug release by IPN-structured hydrogel.

The Kurisawa Reference teaches a method wherein the drug was incorporated into the hydrogel as the chemical reaction was being carried out to form the Dex polymer network. In contrast, the current method avoids using a chemical reaction for loading the drug, because the chemical reaction could damage the drug or influence its activity. In the present invention, drug is mixed into the aqueous dispersion of IPN hydrogel nanoparticles at room temperature, at which the

dispersion was a liquid. The drug is then embedded into the between the hydrogel nanoparticles as the temperature was raised to above 34°C where the dispersion becomes a solid gel by physical hydrophobic interaction.

Figure 16 of the instant application shows a schematic diagram of how the physically bonded nanoparticle network is formed above the gelation temperature. (a) There are small sized pores with the size determined by interparticle spacing and the large sized pores with the size determined by the number of surrounding particles. (b) The nanoparticle network formed by mixing small and large particles. The small particles can fill in either the interstitials between particles or large pores, slowing down the release of drug molecules. Again, no chemical reaction is required to load drug in the present invention, in contrast with the methods taught in the Kurisawa Reference.

The loading method taught in the current specification has the additional advantage that the drug loaded inside gelled hydrogel nanoparticles can be released naturally at body temperature without requirements of one or two enzymes as required in the method of the Kurisawa Reference.



The Examiner states that further motivation can be found in the Qiu Reference, which teaches the common characteristics of temperature sensitive polymers is the presence of hydrophobic groups, and by using different monomers the lower critical solution temperature (LCST) of temperature sensitive polymers can be altered (p.323, 1st column, last paragraph, and 2nd column 1st paragraph). Qiu et al. further teach as the polymer chain which contains more hydrophobic constituents, LCST becomes lower, and the LCST can be changed by adjusting the ratio of hydrophilic and hydrophobic segment of the polymer (p.324, 1st column, lines 8-12).

Applicants acknowledge that the Qiu Reference teaches that the relationship between LCST and hydrophobic groups may be extended to hydrophobic interaction. From this description, one can further see that the PAAm/PAAc IPN particles of the Bouillot Reference, cited by the examiner, have no the LCST and therefore cannot have hydrophobic interaction to form a solid gel above the LCST.

The Examiner states that the Qiu Reference teaches that if the polymer chains in hydrogels are not covalently cross-linked, temperature-sensitive hydrogels may undergo sol-gel phase transitions instead of swelling-shrinking transitions. The thermally reversible gels with inverse temperature dependence become sol at higher temperatures. Qiu et al. teach temperature-sensitive hydrogels can also be made using temperature sensitive crosslinking agents (p.324, 2nd column, 1st and 2nd paragraphs). It must be noted that a polymer above the critical concentration (called critical gel concentration) the gel phase appears.

Applicants respectfully point out that the Qiu Reference is describing the gelation of polymer chains. Polymer chains are entirely distinct from the IPN hydrogel nanoparticles of the current application, both in the way that they are synthesized, and the behavior of the final products. For example, gelled copolymer chains at an elevated temperature can only have one mesh size, which is determined by the distribution of polymer chains. In significant contrast, the gelled IPN hydrogel nanoparticles in water which are taught in the instant application have two mesh sizes a body temperature because there are two different networks in gelled nanoparticles. The primary network is crosslinked polymer chains inside each nanoparticle, while the secondary network is a crosslinked system of the nanoparticles themselves. The mesh size of the primary network depends on the concentration ratio of the crosslinker to linear polymer chains or monomers and is usually around from 1 to 10 nm. In comparison, the mesh size of the secondary network depends on the concentration of the crosslinker and nanoparticles, and the size of nanoparticle. The mesh size is typically around from 50 to 500 nm.

Therefore, a person of ordinary skill in the art at the time the invention was made would not have been motivated or able to practice the currently claimed invention, because gelation by the hydrophobic interaction among the polymer chains is not sufficient on its own. For example, pure

PNIPAM nanoparticles, which certainly have hydrophobic interactions among the polymer chains, do not have a sol-gel transition at LCST.

One aspect of the novelty of the present invention is that it has incorporated PAAc to form a second polymer network which interpenetrates the first PNIPAM network. It is PAAc, a temperature- insensitive component, that does not shrink with increasing temperature. As result, the PAAc network supports the PNIPAM network so that the PNIPAM network can't completely collapse at and above the LCST. Because the PNIPAM network is supported even above the LCST, its size does not change and the distance between the neighboring particles is close enough so that the hydrophobic interaction can exist between neighboring particles.

The Examiner also states that a person of ordinary skill in the art at the time the invention was made could have been motivated to mix the isolated IPN of mono-dispersed nanoparticles as taught by Bouillot et al. with a biologically active material at a temperature which is below the gelation temperature (Tg) of the IPN of mono-dispersed nanoparticles according to the teachings of Kurisawa et al. with predictable results.

Applicants respectfully disagree. In the method taught in the Kurisawa Reference, the drug was added during a chemical reaction when the formation of the Dex polymer network was carried out. The present invention seeks to avoid adding the drug during a chemical reaction, because it could damage the drug. In the present invention, the drug is mixed into the aqueous dispersion of IPN hydrogel nanoparticles at room temperature, at which the dispersion is a liquid. The drug is then embedded into the between the hydrogel nanoparticles as the temperature is raised to above 34°C, where the dispersion becomes a solid gel due to the physical hydrophobic interaction.

C. Claims 15-20 over Bouillot in view of Jones in further view of Soane

The Examiner has rejected Claims 15 and 23 under 35 U.S.C. 103(a) as being unpatentable over the Bouillot Reference in view of Jones et al. (Macromolecules, 2000, Vol. 33, p.8301-8306, "the Jones Reference") and further in view of Soane (US Patent No. 5,135,627, "the Soane Reference").

The Examiner states that the Bouillot Reference teaches the limitations of Claim 15, and does not teach the use of SDS as a surfactant or potassium persulfate as the initiator. However, the Examiner states that the Jones Reference teaches synthesis of hydrogel nanoparticles using SDS (p.8301 2nd column 2nd paragraph). The Examiner goes on to state that the Soane Reference teaches potassium persulfate may be substituted for ammonium persulfate as an initiator (column 6 lines 5-8).

As described in detail above, the Bouillot Reference teaches the synthesis of polyacrylamide (PAAm) particles, not poly-N-isopropylacrylamide (PNIPAM) particles as currently claimed. PAAm and PNIAPAM are very different particles, both in terms of the way they can be synthesized (inverse microemulsion polymerization versus precipitation polymerization), and the properties they possess (e.g. swelling in response to increased temperature). Therefore, the teaching of the Bouillot Reference, which relates to PAAm, would not have provided a motivation to one of skill in the art to use PNIPAM.

The use of SDS as a surfactant or potassium persulfate as the initiator as described in the Jones Reference would not have provided the necessary motivation to one of skill in the art to make this unrelated inventive step.

An inventive concept of the current claims is that PNIPAM/PAAc IPN hydrogel nanoparticles have been synthesized, and that these hydrogel nanoparticles have temperature induced hydrophobic interaction. Below the LCST, the hydrophobic interaction is turned off, and the dispersion of the hydrogel nanoparticles is a liquid. As the temperature was raised above the LCST, the hydrophobic interaction is turned on to allow the INP nanoparticles to stick together to form a solid gel. So far, the available publications with so many different combinations of common chemicals have not been able to produce our novel dispersion of IPN hydrogel nanoparticles. This further demonstrates our invention is unique, and could not be obtained by others in the art.

D. Claims 15 and 27 over Cai in view of Bouillot

The Examiner has rejected Claims 15 and 27 under 35 U.S.C. 103(a) as being unpatentable over the Cai Reference in view of the Bouillot Reference. The Examiner states that Claims 15 and 27 are drawn to a method of preparing an IPN comprising, providing a first polymer nanoparticle

prepared by mixing first monomer, a surfactant, a first cross linking agent, and first initiator at a first temperature, adding to the first monodispersed polymer nanoparticles a second monomer, a second cross linking agent, a second initiator and an activator, mixing the nanoparticles solution for a period of time at a second temperature, isolating the IPN nanoparticles, and the second temperature is about 70°C.

The Examiner states that the Cai Reference teaches a method of preparing monolithic bulk hydrogels with microstructure (BHM) and a method of forming an interpenetrating polymer network (IPN) (p.173 Figure 2 and 1st column), comprising, synthesizing microgel particles (providing a dispersion of first polymer nanoparticles) by mixing a first monomers poly(-N-isopropylacrylamide) (NIPAAm) and acrylic acid (AA) in appropriate molar ratios without a surfactant, a cross linking agent BIS (or N, N'-methylenebisacrylamide), the solution was purged under N_2 for half an hour, the initiator APS (potassium persulfate) was added and the reaction temperature was maintained 65°C temperature (at about 70°C), the reactions were allowed to proceed for 6 to 8 hours and the mixture is kept overnight at room temperature for completion of the reaction (p.171 1st column last paragraph and 2nd column 1st paragraph). The Examiner states that the Cai Reference further teach the NIPAAm monomer, microgel solution, and cross linker BIS were mixed in a bottle, the solution were shaken for 20 minutes fro complete dissolution of the monomers and then purged with N_2 for 20 minutes for the removal of the oxygen then the initiators APS and SBS (second initiator) were added to the reaction mixture and polymerized at room temperature (at about 21°C) for 24 hours reaction, formed bulk hydrogels were cut and washed to remove unreacted monomer (isolating the hydrogels), (p.171 1st and 2nd column 2nd paragraph). The Examiner states that the Cai Reference teaches surfactant free emulsion polymerization (p.171 last paragraph).

The Examiner states that the Cai Reference does not teach a surfactant. However, the Soane Reference teaches a surfactant such as SDS can be used to stabilize the dispersion (column 7 lines 10-11).

The Examiner has cited many paragraphs from the Cai Reference. However, the basic fact is that the Cai Reference teaches a bulk gel. As the Cai Reference teaches in the abstract: "A new method was used for the production of fast-responding **bulk hydrogels with microstructure (BHMs)** with a high swelling ratio." This is reiterated several times, including on p. 171 2nd column

3rd paragraph, "**Formation of the BHM.** The NIPAAm monomer, microgel solution, and crosslinker BIS were mixed in a 50-mL, round-bottom bottle." Again, on p. 173 2nd column lines 12-17, "(o)n the basis of this ideal, we propose that when the monomer NIPAAm is mixed with the NIPAAm-AA microgel solution and crosslinker, the ionic microgel particles can be crosslinked with one another and into the bulk matrix, **forming a BHM** (Fig. 2)."

The key steps taught in the Cai Reference are that NIPAM-AA microgels are crosslinked into a NIPAM bulk gels as shown in Fig. 2 of the Cai Reference. The IPN concept was introduced because the NIPAM of the bulk gel was interpenetrating with NIPAM-AA microgel network.

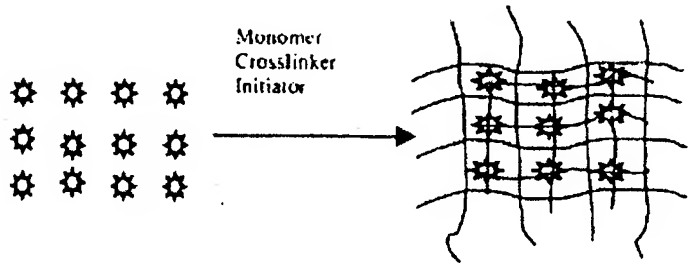
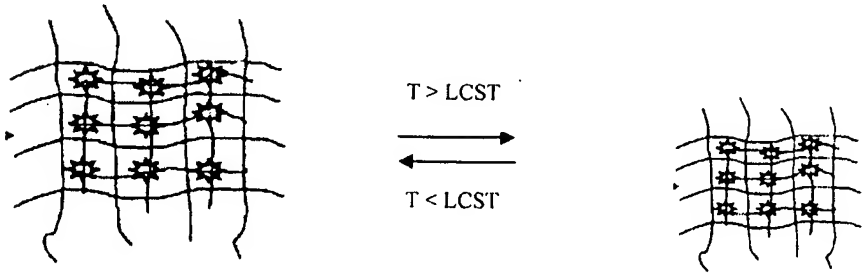


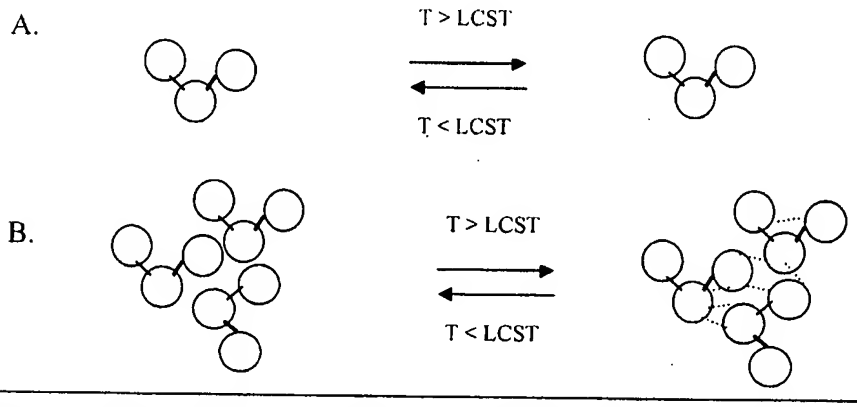
Figure 2 Schematic illustration of the formation of a BHM based on microgel particles.



By switching the temperature below or above the LCST of PNIPAM, the authors of the Cai Reference studied the swelling behavior of this BHM and used BHM to isolate a biologically active (bovine serum albumin, a protein) material. From the figure above according to the authors' description in the reference, although the BHM shrank above the LCST, it was a single piece of the bulk gel below or above the LCST.

In contrast, the currently-claimed IPN hydrogel nanoparticles have two interpenetrating polymer networks of PNIPAM and PAAc for each individual nanoparticle and have nothing to do with a bulk gel. The nanoclusters of current Claims 29-40 and 41-47 are physically (Claims 29-40) or chemically (41-47) bonded with neighboring IPN hydrogel nanoparticles as shown in **Schematic 3** below:

Schematic 3. Bonding of nanoclusters in the current claims.



A: a nanocluster with 3 chemically bonded IPN hydrogel nanoparticles above the LCST of the PNIPAM using
B: nanoclusters can be used as building blocks to form a solid gel above the LCST due to hydrophobic interaction between nanoclusters (dotted bars). The dispersion of nanoclusters become a liquid when the hydrophobic interaction (dotted bars) was turned off below the LCST. The chemical bond inside an individual nanocluster (solid bars) was not changed with temperature.

The Examiner states that the Cai Reference does not teach the first cross-linking agent comprises EDAC and second cross linking agent comprises adipic acid dihydrazide, heating at a first temperature about 44°C, for about 25-45 min (33-37 min). However, Hennink & Nostrum teach EDC or EDAC, and that swelling and degradation of the gels could be controlled by the amount of adipic acid dihydrazide. Moreover, routine experimentation is widely used by one of ordinary skill in the art to determine optimum or workable ranges of particular parameters such as temperature, time, and the type and amount of cross linking agent in a polymerization reaction.

The current application is the first to use adipic dihydrazide as a crosslinker to link a few hydrogel nanoparticles to form a nanocluster. The use in the Cai Reference only involved embedding microgels in a bulk gel and had nothing to do with nanoclusters.

Therefore, neither the Cai Reference, nor the Bouillot Reference, alone or in combination, could provide one of skill in the art with sufficient teaching to practice the currently claimed invention.

E. Claims 29-40 and 41-47 over Cai in view of Hennink

The Examiner has also rejected Claims 29-40 and 41-47 under 35 U.S.C. 103(a) as being unpatentable over the Cai Reference in view of the Hennink Reference.

The Examiner has stated that Claims 29-40 are drawn to a method of preparing a nanocluster of cross-linked IPN nanoparticles comprising, providing a dispersion of IPN nanoparticles, adding a first cross linking agent and a second cross linking agent to the dispersion of the IPN nanoparticles, heating the IPN cross linking solution to a first temperature for a period of time, wherein the IPN nanoparticles have uniformed size and comprise a first polymer network interpenetrating a second polymer network, mixing the nanocluster of crosslinked IPNs with a biologically active material at a second temperature, the first polymer comprises of poly(-N-isopropylacrylamide) and the second polymer comprises poly(acrylic acid), first cross-linking agent comprises EDAC and second cross linking agent comprises adipic acid dihydrazide, heating at a first temperature, about 44°C, for about 25-45 min (33-37 min), mixing cross-linked IPNs with a biologically active material at about 33°C, and hydrodynamic radius in the range from 225 nm to about 240 nm.

The Examiner states that Claims 41-47 are drawn to a nanocluster of cross-linked IPN nanoparticles comprising: at least two IPN nanoparticles linked by a cross-linking group, a first polymer network interpenetrating a second polymer network, the cross linking group is adipic acid dihydrazide, wherein each IPN nanoparticles have a uniformed sized and an have an average hydrodynamic radius of nanoparticles is in the range of 155 nm to about 1000 nm.

As described in detail above, the Cai Reference teaches embedding microgels in a bulk gel and is unrelated to the currently-claimed nanocluster technology. Any teaching from the Hennink

Reference regarding controlling the swelling and degradation of gels using the amount of adipic acid dihydrazide would not provide the necessary motivation or teaching to allow one of skill in the art to practice the invention.

Therefore, neither of the cited references, alone or in combination, would have provided the necessary information to one of skill in the art to allow them to practice the claimed invention. Claims 29-40 and 41-47 are therefore non-obvious and in condition for allowance.

IV. Conclusion

Applicants respectfully submit that, in light of the foregoing comments and amendments, all pending claims are now in condition for allowance. A Notice of Allowance is therefore requested.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

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Date